The impact of gender on outcome after infrainguinal arterial reconstructions for peripheral occlusive disease

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Objective: **The role of gender on the outcome of infrainguinal arterial revascularization (IAR) for peripheral arterial occlusive disease remains uncertain. This study analyzed the outcome of IARs performed over 15 years, stratifying the results by sex.**

Methods: **Details of consecutive patients undergoing primary IAR for peripheral arterial occlusive disease from 1995 to 2009 at our institution were prospectively stored in a vascular registry. Demographics, risk factors, indications for surgery, inflow sources, outflow target vessels, types of conduit, and adverse outcomes were analyzed. Postoperative surveillance included clinical examination supplemented with duplex scans and ankle-brachial index measurements in all patients at discharge, 30 days, 6 months, and every 6 months thereafter. End points of the study, ie, patency, limb salvage, and survival rates, were assessed using Kaplan-Meier life-table analysis. The χ^2 or Fisher exact, Student *t*, and log-rank tests were used to establish statistical significance.**

Results: **Our sample consisted of 1459 IARs performed in 1333 patients, comprising 496 women (37.2%; 531 IARs), who were a mean 3 years older than the men (74 vs 71 years; $P < .001$) and had a higher incidence of diabetes mellitus (52% vs 46%; $P = .03$) and surgery for limb salvage (91% vs 87%; $P = .02$). An autogenous vein conduit (great or small saphenous, or both, spliced, arm, or composite veins) was used in 87% of the IARs. No deaths occurred perioperatively (30 days). The major and minor complication rates were comparable between men and women. At 10 years, the primary patency rate was 47% in women vs 49% in men ($P = .67$), the assisted primary patency rate was, respectively, 53% vs 50% ($P = .69$), the secondary patency rate was 61% vs 61% ($P = .66$), limb salvage rate was 93% vs 91% ($P = .54$), and survival rate was 43% vs 49% ($P = .65$). Stratifying by type of conduit revealed no differences in patency or limb salvage rates.**

Conclusions: **Despite an older age and more advanced stages of disease on presentation in women, IAR performed in women can achieve patency and limb salvage rates statistically no different from those recorded in their male counterparts, supporting the conviction that sex per se does not influence the outcome of lower extremity revascularization. (J Vasc Surg 2012;56:343-52.)**

The incidence of peripheral arterial occlusive disease (PAD) is rising, along with the increase in life expectancy and the prevalence of atherosclerosis, and is responsible for high cardiovascular morbidity and mortality rates.[1] Women have generally been assumed to have a lower prevalence of PAD than men, and this may be true to some extent for women before or early into menopause, probably related to the "atheroprotective" effects of hormonal and metabolic factors in premenopausal women, although the mechanisms behind them are not well understood.[2,3] PAD in women increases significantly during and after menopause, however, and its incidence in women and men in their 6th and 7th decades is virtually identical.[4] Recent community-based surveys have even reported higher rates of PAD in women than in men.[5,6]

Several large studies have shown that (1) increasing proportions of patients treated for PAD are women, (2) women are more likely to be older at presentation, and (3) women undergoing infrainguinal arterial reconstruction (IAR) tend to have more advanced disease than their male counterparts.[7,8] The numerous studies on the outcome of IAR in women and men have reported conflicting data and widely varied conclusions about this issue:

- Some authors found no significant differences between women and men in long-term IAR patency[7-12] and limb salvage rates,[9,11-15] whereas others identified worse long-term IAR patency rates for women as a whole[7,13,15,16] or in a subset of IARs to the tibial vessels.[14]
- Perioperative mortality did not differ between women and men in most studies,[8-13] but rates for myocardial infarction (MI) or wound complications were significantly higher for women in all series reporting morbidity.[8,10-12,14]
- Many studies found no differences in long-term survival between women and men,[7-9,12,14,15] but others reported worse long-term survival rates in women,

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with statistically significant differences, especially for women with diabetes mellitus (DM).[10,13]

In the light of such evidence, it has been hard to draw any final conclusions on the effect of sex on the outcome of IAR. Our question was whether women with infrainguinal disease have worse outcomes in patency, limb salvage, and long-term survival rates than their male counterparts after IAR. This study aims to address this question.

METHODS

Details of all consecutive patients undergoing primary IAR at our institution between 1995 and 2009 for PAD were prospectively stored in a vascular registry. The data included patient demographics, risk factors, indication for revascularization, inflow source, outflow target vessel, type of conduit, and adverse outcomes.

All patients had an electrocardiogram, and any history of MI, congestive heart failure, or angina, was recorded. If clinical history and electrocardiogram findings were normal, no further work-up was undertaken; if either were abnormal, echocardiogram or dipyridamole thallium scan, or both, were obtained at our consultant cardiologist's discretion. All patients underwent preoperative standard biplanar arteriography, magnetic resonance angiography, or computed tomography angiography (CTA), or a combination of these methods, to confirm the clinical and vascular laboratory diagnosis of PAD, as determined by arterial mapping with duplex ultrasound imaging and measurement of the ankle-brachial index (ABI), and to plan surgery. All patients with foot lesions were treated according to a standard protocol.[17]

Surgical technique. Revascularizations were completed using a single-team approach for arterial dissection and vein harvesting when an autologous vein was used. The preferred conduit was the great saphenous vein (GSV), which was harvested whenever this seemed feasible on the strength of venous mapping by duplex scan (subject to direct assessment at surgery). The reversed GSV bypass was the preferred procedure, exclusively for a personal choice of the surgeon. When the ipsilateral or contralateral GSV was unsuitable or not wholly available, and spliced veins (great/small saphenous vein and arm vein) were also unavailable, then a 7- or 8-mm thin-walled expanded polytetrafluorethylene (PTFE) graft (Gore-Tex; W. L. Gore and Associates, Flagstaff, Ariz) was used. Short bypass revascularizations were performed when the surgeon found the superficial femoral artery or the popliteal artery was adequate for inflow (confirming preoperative angiographic findings). The selected inflow artery was exposed in standard fashion.

The distal exposure methods varied, depending on the vessel chosen for the bypass procedure. The inframalleolar vessels include the posterior tibial artery, at or below the medial malleolus, the dorsalis pedis artery, and the pedal branch arteries, defined as any tarsal, plantar, or anterior lateral malleolar artery.[18] The peroneal artery was always exposed using a lateral approach requiring segmental fibulectomy.[19] The dorsalis pedis artery was often chosen as the outflow target artery as an alternative to a patent peroneal artery and when no tibial vessels were in direct continuity with the foot. Revascularization to the dorsalis pedis artery was avoided in cases of severe dorsal foot infection.

All distal anastomotic sites below the knee underwent standard vein patch angioplasty no longer than 3 cm, as described elsewhere.[20] The vein for the patch was harvested from any available site, including saphenous vein remnants, arm veins harvested under local anesthesia, and occasionally saphenous vein collaterals. When the anterior tibial artery or the peroneal artery were used as the outflow vessel, the vein graft was always routed through the interosseous membrane but was routed in the standard fashion when the posterior tibial artery was used.

All revascularizations were performed with the patient under regional anesthesia (epidural or spinal). No intraoperative contrast or duplex scan arteriography was performed. Intravenous heparin (5000 IU) was administered before clamping and was not reversed with protamine. Heparin infusion was started 6 to 10 hours postoperatively, with oral warfarin (Coumadin; Du Pont De Nemours, Wilmington, Del) administered on the first postoperative day. Long-term anticoagulation treatment with Coumadin was continued for 6 months, aiming for a normalized ratio of between 2 and 3 in most of the patients. After 6 months, 325 mg aspirin was taken daily.

Postoperative surveillance. End points of the study were primary patency, assisted primary patency, secondary patency, limb salvage, and long-term survival rates. Postoperative surveillance included clinical examinations, supplemented with duplex scans and ABI measurements at discharge, 30 days, 6 months, and every 6 months thereafter. Follow-up always included a color duplex investigation of the inflow artery, the whole conduit, both anastomoses, and the initial tract of the outflow artery. Graft patency was assessed from the presence of a palpable distal pulse, ABI measurement, or a patent graft on duplex scan. A drop in the ABI of >0.15 compared with the initial postoperative index was assumed to indicate a failing graft. A duplex ultrasound scan was indicative of a significant lesion along the graft if the peak systolic velocity was >300 cm/s and the velocity ratio was >3.0, whereas the absence of any color flow in the graft was indicative of occlusion. Graft stenoses discovered by duplex scan were confirmed by arteriography or CTA and electively repaired if the diameter reduction was $>50\%$, judging from the image.

After surgery, patients were seen as often as necessary until their wound healed completely. The wound-healing process was assessed in terms of wound-related complications (ie, the need for hospital readmission or repeat surgery, or additional wound-related treatment such as antibiotics or a visiting nurse) and the time it took for the wound to heal. The healing times for surgical incisions and for ischemic wounds requiring arterial reconstruction were recorded separately. The total ischemic wound-healing time included secondary procedures needed to treat ischemic ulcers or gangrene, including debridement or toe amputation. Minor toe and foot amputations or debride-

Table I. Demographics, risk factors, and comorbidities

Variable[a]	*Total*	*Group I*	*Group II*	P
IARs	1459 (100)	531 (36.4)	928 (63.6)	
Patients	1333 (100)	496 (37.2)	837 (62.8)	
Age, years		74 ± 5.4	71 ± 6.8	<.001
Diabetes mellitus	647 (48.5)	259 (52.2)	388 (46.3)	.03
Hyperlipemia	810 (60.7)	287 (57.8)	523 (62.5)	.10
Hypertension	870 (65.2)	303 (61.1)	567 (67.7)	.01
Smoking history[b]	713 (53.5)	218 (43.9)	495 (59.1)	<.001
Chronic kidney disease[c]	145 (10.8)	46 (9.2)	99 (11.8)	.14
Cardiac disease	683 (51.2)	239 (48.2)	444 (53.0)	.09
Prior intervention				
PTA stenting/CABG	266 (19.9)	91 (18.3)	175 (20.9)	.26
Inflow procedures	220 (16.5)	65 (13.1)	155 (18.5)	.01
History of				
Myocardial infarction	368 (27.6)	132 (26.6)	236 (28.2)	.53
Pulmonary disease	224 (16.8)	80 (16.1)	144 (17.2)	.61
Stroke	146 (10.9)	49 (9.9)	97 (11.6)	.33
ABI measurement				
In claudication		0.75 ± 0.27	0.77 ± 0.19	.09
In critical limb ischemia		0.42 ± 0.29	0.45 ± 0.33	.07

ABI, Ankle-brachial index; *CABG,* coronary artery bypass grafting; *IAR*, infrainguinal arterial revascularization; *PTA,* percutaneous transluminal angioplasty.
[a]Continuous data are shown as the mean ± standard deviation and categoric data as number (%).
[b]Current tobacco use or cessation within the last 5 years.
[c]Defined as creatinine >2.0 mg/dL.

ment performed after the arterial reconstruction to complete the treatment of the original ischemic lesions were considered as part of the primary operation rather than as redo surgery. All the criteria used for this analysis aimed to conform to the standards suggested by the Ad Hoc Committee of the Joint Council of Vascular Societies for Reports Dealing with Lower Extremity Ischemia.[21]

Statistical analysis. Continuous data were compared with the Student *t*-test. Frequencies and categoric data were compared with a χ^2 or Fisher exact test, as appropriate. The primary patency, assisted primary patency, secondary patency, limb salvage, and long-term survival rates were assessed by Kaplan-Meier analysis, and curves were compared using the Mantel-Cox log-rank test. A Cox proportional hazard analysis was used to determine which factors with statistical or marginal significance at univariate analysis could influence outcomes, calculating the odds ratio (OR) with 95% confidence intervals (CIs). All tests were two-tailed, and statistical significance was inferred at value of $P < .05$. Because each perioperative and late outcome was correlated with the surgical procedure, and patients who underwent bilateral IAR were exposed to twice the risk of graft failure or limb loss, several data items were analyzed vis-à-vis surgical procedures instead of patients.

RESULTS

During a 15-year period, 1459 IARs were performed in 1333 patients at our institution, comprising 531 IARs in 496 women (37.2%; group I) and 928 IARs in 837 men (group II). Staged bilateral IARs were performed in 126 patients (35 in group I). An additional 45 patients referred to our center who were mentally impaired (n = 34) or had a life expectancy of <1 year (n = 11), who were bedridden or nonambulatory, and 19 patients with ischemic soft tissue breakdown between the calcaneus and metatarsal heads (plantar region) were not considered for arterial reconstructive surgery. These 45 patients had necrotic ulcers or gangrene and 33 required primary amputation to treat their disease; the other 12 underwent a major amputation generally ≤30 days after a percutaneous intervention had failed. Among the 19 patients with extensive tissue loss in the plantar region, 13 underwent early (≤30 days) and six delayed major amputation after a primary percutaneous intervention had failed.

Table II. Indication for infrainguinal arterial reconstruction

Indication	*Total* *No. (%)*	*Group I* *No. (%)*	*Group II* *No. (%)*	P
Claudication	168 (11.5)	48 (9.1)	120 (12.9)	.02
Critical limb ischemia	1291 (88.5)	483 (90.9)	808 (87.1)	.02
Rest pain	455 (31.2)	179 (33.7)	276 (29.7)	.11
Nonhealing ulcer	509 (34.9)	198 (37.3)	311 (33.5)	.14
Gangrene	327 (22.4)	106 (19.9)	221 (23.8)	.09

Table I summarizes demographics, risk factors, comorbidities, and other variables in both groups. The women were significantly older than the men at presentation (74 ± 5.4 vs 71 ± 6.8; $P < .001$) and were more likely to have DM (52.2% vs 46.3%; $P = .03$), whereas the men more commonly had a history of smoking (59.1% vs 43.9%; $P < .001$), arterial hypertension (67.7% vs 61.1%; $P = .01$), and prior inflow procedures (18.5% vs 13.5%; $P = .01$). There were no differences between the two groups in the other considered variables (Table I). The most common indica-

Table III. Inflow sources, outflow target vessel, type of conduit, and preoperative foot procedures

Variable	*Total* No. (%)	*Group I* No. (%)	*Group II* No. (%)	P
Inflow sources				
Iliac/graft	217 (14.8)	75 (14.1)	142 (15.3)	.54
Common femoral artery	733 (50.2)	276 (51.9)	457 (49.2)	.31
Deep femoral artery	78 (5.3)	29 (5.4)	49 (5.2)	.88
Distal SFA/AK popliteal	248 (17.0)	86 (16.2)	162 (17.4)	.53
BK popliteal	125 (8.5)	48 (9.0)	77 (8.3)	.62
TPT/tibial	58 (3.9)	17 (3.2)	41 (4.4)	.25
Outflow vessel target				
AK popliteal	365 (25.0)	141 (26.5)	224 (24.1)	.30
BK popliteal/TPT	360 (24.6)	141 (26.5)	219 (23.6)	.20
Tibial	533 (36.5)	181 (34.1)	352 (37.9)	.14
Proximal third	269 (18.4)	94 (17.7)	175 (18.8)	.58
Midthird	106 (7.2)	35 (6.6)	71 (7.6)	.45
Distal third	158 (10.8)	52 (9.8)	106 (11.4)	.33
Inframalleolar artery	201 (13.8)	68 (12.8)	133 (14.3)	.41
Bypass procedure conduit				
Reversed autogenous GSV	1163 (79.7)	433 (81.5)	730 (78.7)	.18
In situ	24 (1.6)	7 (1.3)	17 (1.8)	.45
Spliced vein (GSV, SSV, arm)	39 (2.6)	12 (2.2)	27 (2.9)	.46
Composite (vein/PTFE)	46 (3.1)	17 (3.2)	29 (3.1)	.93
PTFE	187 (12.8)	62 (11.6)	125 (13.4)	.32
Preoperative foot care				
Drainage	162 (11.1)	51 (9.6)	111 (11.9)	.17
Debridement	211 (14.4)	66 (12.4)	145 (15.6)	.09

AK, Above the knee; *BK,* below the knee; *GSV,* great saphenous vein; *PTFE,* polytetrafluoroethylene; *SFA,* superficial femoral artery; *SSV,* small saphenous vein; *TPT,* tibial-peroneal trunk.

tion for surgery (Table II) was critical limb ischemia (CLI, 90.9% in group I vs 87.1% in group II; P = .02) in the subset of rest pain (33.7% vs 29.7%; P = .11), nonhealing ulcer (37.3 vs 33.5%; P = .14), or gangrene (19.9% vs 23.8%; P = .09). In both groups, the most common inflow sources were the common femoral artery and the superficial femoral artery/above-knee popliteal artery (51.9% and 16.2%, respectively, in group I; 49.2% and 17.4% in group II). The tibial arteries were the more often used target outflow vessels in group I (34.1%) and group II (37.9%; Table III). The reversed autogenous GSV was the preferred graft for revascularization in 81.5% of women and in 78.7% of men. There was no difference between the sexes in the use of in situ or spliced veins or in composite or prosthetic conduits (Table III).

Perioperative mortality and morbidity data. A detailed list of the perioperative outcomes is given in Table IV. There were no perioperative deaths. The overall rates for systemic and minor complications, additional local procedures, and minor amputations were comparable between the two groups. No differences emerged between groups I and II in improvement in the postoperative ABI measurements.

Long-term outcomes. Of the 1333 patients alive 30 days after IAR, 38 (2.8%, 38 IARs) were lost to follow-up. The follow-up was therefore completed by 1295 patients (97.2%, 1421 IARs), of which 484 were women (519 IARs). The median follow-up was 6.1 years in group I (mean, 7 ± 2.2; range, 0.1-15 years) and 6.4 years in group II (mean, 7.2 ± 2.6; range, 0.1-15 years).

To establish whether prosthetic graft revascularizations might influence the technical outcome, we stratified the two groups by vein vs prosthetic grafts. Figs 1-4 show details of Kaplan-Meier life-table analyses of the primary patency, assisted primary patency, secondary patency, and limb salvage rates for groups I and II, as a whole and after stratifying patients by type of conduit.

At 5 and 10 years, the overall primary patency rates were, respectively, 68% and 47% in women and 71% and 49% in men (log-rank test, P = .67; Fig 1), with no significant difference between the two groups for vein grafts (70% and 50% vs 73% and 51%; log-rank test, P = .64) or prosthetic grafts (42% and 21% vs 46% and 19%; log-rank test, P = .71).

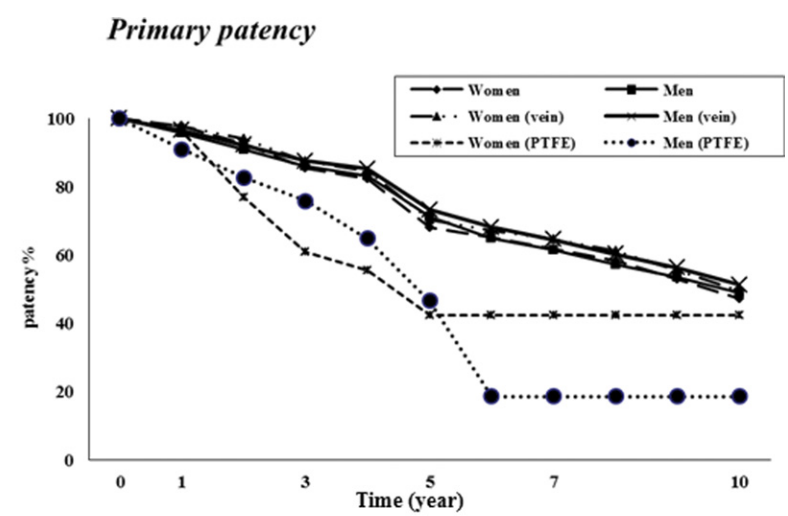
At 5 and 10 years, the overall assisted primary patency rates were, respectively, 76% and 53% in women and 77% and 50% in men (log-rank test, P = .69; Fig 2), with no significant difference between the two groups for vein grafts (77% and 55% vs 79% and 51%; log-rank test, P = .64) or prosthetic grafts (61% and 30% vs 70% and 35%; log-rank test, P = .96). All involved lesions were detected on duplex imaging and were usually intrinsic defects equally distributed along the length of the failing but still patent graft. Graft revisions mainly involved thrombectomy or lysis, or both, percutaneous vein graft dilation, and patch angioplasty.

At 5 and 10 years, the overall secondary patency rates were, respectively, 83% and 61% in women and 83% and 61% in men (log-rank test, P = .66; Fig 3), with no

Table IV. Perioperative (30-day) outcomes

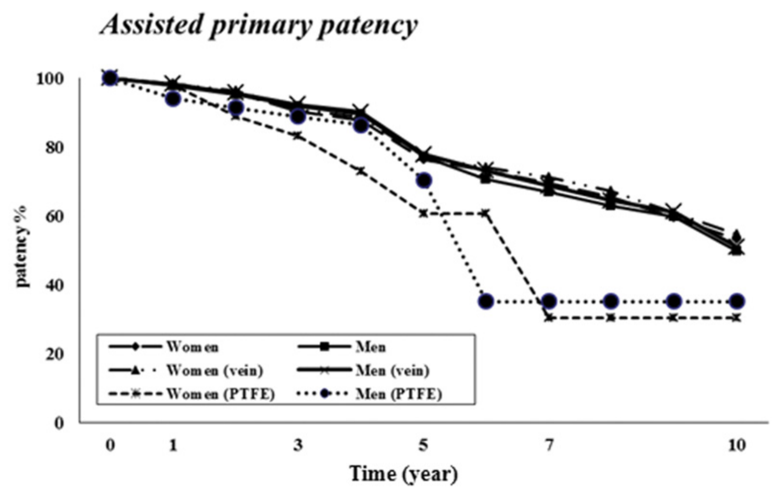
Outcome[a]	*Total*	*Group I*	*Group II*	P
Death	0	0	0	
Major amputation	22 (1.5)	6 (1.1)	16 (1.7)	.37
Systemic complications	202 (13.8)	68 (12.8)	134 (14.4)	.38
Nonfatal MI	36 (2.5)	18 (3.4)	18 (1.9)	.08
Renal failure	26 (1.7)	10 (1.8)	16 (1.7)	.82
Pneumonia	53 (3.6)	15 (2.8)	38 (4.1)	.21
Arrhythmia	87 (5.9)	25 (4.7)	62 (6.7)	.12
Minor complications	112 (7.6)	46 (8.6)	66 (7.1)	.28
Wound hematoma/dehiscence	44 (3.0)	21 (3.9)	23 (2.4)	.11
Inguinal lymphocele	63 (4.3)	24 (4.5)	39 (4.2)	.77
Wound infection	5 (0.3)	1 (0.2)	4 (0.4)	.44[b]
Graft infection		0	0	
Additional local procedures	273 (18.7)	96 (18.0)	177 (19.0)	.63
Drainage	60 (4.1)	25 (4.7)	35 (3.7)	.38
Debridement	213 (14.5)	71 (13.3)	142 (15.3)	.31
Minor amputations	326 (22.3)	105 (19.7)	221 (23.8)	.08
Toe(s), ray(s)	239 (16.3)	81 (15.2)	158 (17.0)	.37
Transmetatarsal	87 (5.9)	24 (4.5)	63 (6.7)	.08
ABI measurement				
In claudication		0.95 ± 0.36	0.96 ± 0.22	.50
In critical limb ischemia		0.82 ± 0.17	0.83 ± 0.13	.20

ABI, Ankle-brachial index; *MI,* myocardial infarction.
[a]Categoric data are shown as number (%) and continuous data are shown as the mean ± standard deviation.
[b]Value derived by the Fisher exact test.



		0	1	3	5	7	10
◆	At risk	519	427	175	92	49	24
	SE ±	0	0.007	0.01	0.04	0.05	0.07
■	At risk	902	784	333	186	103	49
	SE ±	0	0.007	0.01	0.02	0.03	0.09
▲	At risk	465	383	154	81	42	21
	SE ±	0	0.007	0.01	0.04	0.05	0.08
✱	At risk	780	686	284	153	89	41
	SE ±	0	0.006	0.01	0.02	0.03	0.09
- ✱ -	At risk	54	44	21	11	7	3
	SE ±	0	0.02	0.09	0.12	0.13	0.13
●	At risk	122	98	49	33	14	8
	SE ±	0	0.02	0.05	0.10	0.07	0.07

Fig 1. Kaplan-Meier life-table analysis shows the primary patency rate for women and men in the series as a whole (odds ratio [OR], 1.04; 95% confidence interval [CI], 0.83-1.33; log-rank test, $P = .67$) and in patients with a vein graft (OR, 1.05; 95% CI, 0.81-1.38; log-rank test, $P = .64$) or with a polytetrafluoroethylene (*PTFE*) graft (OR, 1.11; 95% CI, 0.62-2.01; log-rank test, $P = .71$). The raw number of the limbs at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup.



◆	At risk	519	430	183	97	52	27
	SE ±	0	0.006	0.01	0.04	0.05	0.08
■	At risk	902	790	341	191	107	53
	SE ±	0	0.005	0.01	0.02	0.03	0.09
▲	At risk	465	383	159	84	44	22
	SE ±	0	0.006	0.01	0.04	0.05	0.08
✕	At risk	780	690	289	156	93	43
	SE ±	0	0.005	0.01	0.02	0.03	0.09
✱	At risk	54	47	24	13	8	5
	SE ±	0	0.01	0.08	0.15	0.18	0.18
●	At risk	122	100	52	35	14	10
	SE ±	0	0.02	0.04	0.09	0.11	0.11

Fig 2. Kaplan-Meier life-table analysis shows the assisted primary patency rate for women and men in the series as a whole (odds ratio [OR], 1.05; 95% confidence interval [CI], 0.80-1.39; log-rank test, $P = .69$) and in patients with a vein graft (log-rank test, $P = .64$; OR, 1.06; 95% CI, 0.79-1.44) or with a polytetrafluoroethylene (*PTFE*) graft (OR, 1.02; 95% CI, 0.44-2.34; log-rank test, $P = .96$). The raw number of the patients at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup.

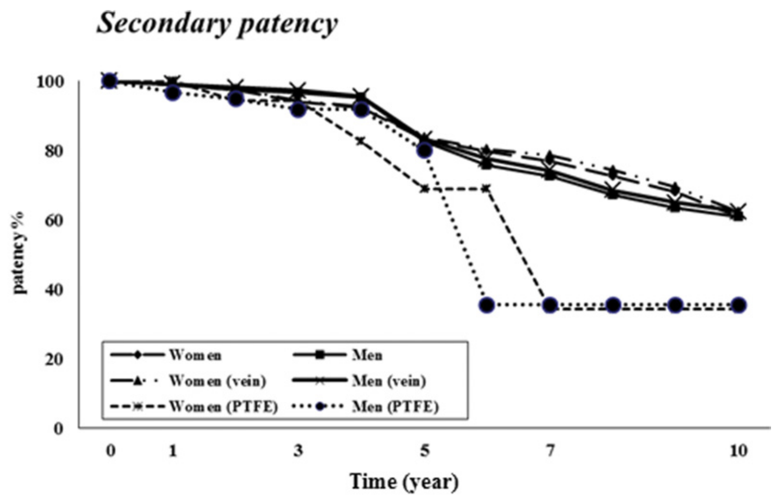
significant difference between the two groups for vein grafts (84% and 62% vs 83% and 62%; log-rank test, $P = .56$) or for prosthetic grafts (69% and 34% vs 80% and 36%; log-rank test, $P = .70$). In most of the grafts that failed, this was due to outflow or inflow disease secondary to myointimal proliferation and hyperplasia or to the progression of atherosclerotic lesions. Graft patency was restored with thrombectomy/lysis, until satisfactory runoff was observed, and distal extension of the revascularization with a "jump" vein graft in the cases of outflow disease or with thrombectomy/lysis and revision (proximal graft extension) in the cases of inflow disease. Some failed IARs were simply thrombectomized or lysed, providing there was no underlying anatomic defect or no atherosclerotic disease adjacent to the graft responsible for graft failure, which was presumably related to a decrease in blood flow in a poor runoff bed.

Overall, 96 major amputations were performed (23% during the perioperative period), with no significant difference between groups I and II (5.9% vs 7.2%; $P = .37$), even after stratifying the groups by vein (5.6% vs 6.9%; $P = .35$) or PTFE graft conduit (9.2% vs 9.0%; $P = .95$). No major amputations were necessary during follow-up of IARs that were above the knee. Seventeen (17.7%) major amputations were needed for persistent foot infections or osteomyelitis, or both, despite a patent graft. Although the major amputation rate was higher in diabetic patients (8.5% vs 5.9%), the difference failed to reach significance ($P = .07$), and there was no statistically significant difference between female and male diabetic patients (8.5% vs 8.2%; $P = .99$) or between female and male nondiabetic patients (3.8% vs 7.1%; $P = .08$).

At 5 and 10 years, the overall limb salvage rates were, respectively, 93% and 93% in women and 92% and 91% in men (log-rank test, $P = .54$; Fig 4), with no significant difference between the two groups for vein grafts (93% and 93% vs 92% and 92%; log-rank test, $P = .48$) or for prosthetic grafts (77% and 77% vs 81% and 81%; log-rank test, $P = .64$).

At 5 and 10 years, patient survival rates were, respectively, 64% and 43% in women and 62% and 49% in men (log-rank test, $P = .65$). The main known cause of death in both groups was cardiac disease.

All potentially prognostic variables, including age, sex, DM, smoking, hypertension, hyperlipidemia, cardiac disease, prior MI or cardiac surgery, prior stroke or inflow



		0	1	3	5	7	10
◆	At risk	519	433	188	101	56	30
	SE ±	0	0.004	0.01	0.03	0.05	0.09
■	At risk	902	796	348	196	111	55
	SE ±	0	0.004	0.007	0.02	0.03	0.06
▲	At risk	465	385	163	87	47	24
	SE ±	0	0.005	0,01	0.03	0.05	0.09
✱	At risk	790	694	294	160	95	45
	SE ±	0	0.003	0.007	0.02	0.03	0.06
*	At risk	54	48	25	14	9	6
	SE ±	0	0	0.04	0.15	0.19	0.19
●	At risk	122	102	54	36	16	10
	SE ±	0	0.01	0.03	0.9	0.13	0.13

Fig 3. Kaplan-Meier life-table analysis shows the secondary patency rate for women and men in the series as a whole (odds ratio [OR], 1.07; 95% confidence interval [CI], 0.77-1.50; log-rank test, $P = .66$) and in patients with a vein graft (OR, 1.10; 95% CI, 0.78-1.58; log-rank test, $P = .56$) or with a polytetrafluoroethylene (*PTFE*) graft (OR, 0.82; 95% CI, 0.31-2.20; log-rank test, $P = .70$). The raw number of the patients at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup.

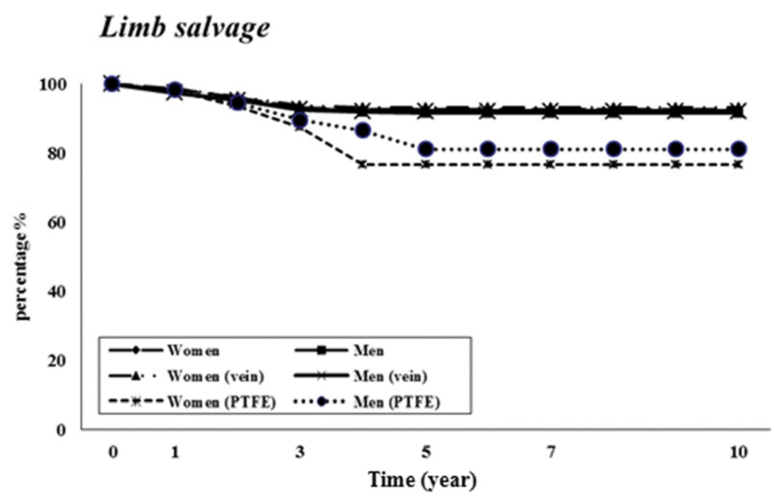
procedures, inflow source and target outflow vessel, and type of conduit, were submitted to univariate analysis as potential predictors of revascularization failure or limb loss. None of these variables influenced the patency or limb salvage rates in either group.

DISCUSSION

The results of IAR for PAD are often difficult to analyze because a multitude of variables may significantly influence the outcome, including (1) different baseline characteristics due to concomitant risk factors and comorbidities, (2) indications for surgery (claudication or CLI), (3) the site of the outflow target artery (above or below the knee popliteal artery, or tibial vessels), and (4) the type and quality of the conduit used (vein or prosthetic graft). Even the role of sex on the outcome of IAR remains hard to establish.

The findings of the present study indicate that female patients can undergo IAR for PAD with patency and limb salvage rates that are statistically no different from those seen in their male counterparts, supporting the conviction that sex per se does not influence the outcome of lower extremity revascularization. The women in our series were significantly older than the men at the time of surgery and had a higher incidence of DM (both these findings are not new in the medical literature[8,9,14,22]), whereas the men were more often past or present smokers and were more likely to have arterial hypertension and a history of prior inflow procedures. No other significant differences emerged between the two groups in risk factors and comorbidities, but prevalence of CLI was higher among women, reinforcing the impression that women are more likely to be referred at an older age than men and treated at a more advanced stage of ischemia.[8,23,24] The reasons for this are likely multifactorial and may include, as suggested in some reports, social isolation, more limited access to care due to financial reasons, and PAD symptoms being mistaken for osteoporosis or arthritis, which are common in such patients.[23,25]

Although >50% of our patients had cardiac disease on presentation, with a high incidence of prior MI and percutaneous transluminal angioplasty/stenting or coronary artery bypass grafting, both in the series as a whole and in each group, the overall rate of perioperative nonfatal MI was only 2.5%, with a higher prevalence among women, though the difference did not reach significance (3.4% vs 1.9%; $P = .08$). A higher frequency of (even fatal) perioperative MI in women was also reported in other analyses, even though men revealed paradoxically more cardiac dis-



	0	1	3	5	7	10
At risk	519	437	191	102	58	32
SE ±	0	0.005	0.01	0.02	0.02	0.02
At risk	902	798	352	198	113	57
SE ±	0	0.005	0.01	0.01	0.01	0.01
At risk	465	387	165	90	49	26
SE ±	0	0.006	0.01	0.02	0.02	0.02
At risk	780	695	296	161	96	47
SE ±	0	0.006	0.01	0.01	0.01	0.01
At risk	54	50	26	12	9	6
SE ±	0	0.02	0.07	0.13	0.13	0.13
At risk	122	103	56	37	17	10
SE ±	0	0.01	0.04	0.09	0.09	0.09

Fig 4. Kaplan-Meier life-table analysis shows the limb salvage rate for women and men in the series as a whole (OR, 0.87; 95% CI, 0.57-1.33; log-rank test, $P = .54$) and in patients with a vein graft (OR, 0.84; 95% CI, 0.53-1.34; log-rank test, $P = .48$) or with polytetrafluoroethylene (*PTFE*) graft (OR, 1.27; 95% CI, 0.42-3.99; log-rank test, $P = .64$). The raw number of the patients at risk and the standard error (*SE*) analyzed for each interval are shown for each subgroup.

ease before surgery, but the investigators were unable to explain why more women had latent cardiac disease going undetected on routine preoperative screening and adversely affecting them postoperatively.[10,26]

Overall, there were no perioperative deaths in our series, a finding never previously reported. Indeed, all other studies recorded overall perioperative mortality rates of 1% to 5%, usually with no differences between women and men.[8-16] Unfortunately, we have no objective data for explaining our remarkable finding, although regional anesthesia (all of our patients underwent epidural or spinal anesthesia, thus minimizing the risk of postoperative major adverse events) and a relatively quick surgical procedure could have also played an important part in this outcome.

Although we might expect the women's more advanced disease at presentation to coincide with technical worse outcomes, this was not true of our sample: female patients fared just as well as their male counterparts in IAR patency and limb salvage rates, even after stratifying by type of conduit. These findings are consistent with other reports on the effect of sex on conventional technical outcome measures,[7-12] but are in contrast with the worse long-term patency rates often identified in women,[7,13,15,16] which have been attributed, for instance, to increased risk factors, such as smoking, DM, older age, and cardiovascular disease, different medical comorbidities, smaller arteries, or late treatment, at more advanced stages of disease.[7,13-16] Unlike an earlier analysis that identified different patency rates at tibial level,[14] but consistently with other authors,[8] we found that performing IARs with tibial arteries as target outflow vessels did not significantly affect the long-term patency and limb salvage rates in our two groups and subgroups, confirming previous findings of ours reported elsewhere.[17,19,20] Adopting an intensive postoperative protocol of graft surveillance led to many prophylactic lesion revisions being performed successfully in both sexes, explaining the marked improvement in the patency rates for failing (assisted primary patency) and failed revascularizations (secondary patency) at all intervals in both groups.

Further features of our study were that (1) the surgical technique involved standard vein patching of all distal anastomotic sites below the knee and (2) all patients received anticoagulation therapy in the postoperative period, regardless of the conduit used. Coumadin therapy has been described as an important factor in improving the patency rates of bypass prosthetic grafts in patients needing arterial reconstruction to infrapopliteal vessels,[27] whereas the long-term benefit of anticoagulation after vein IAR remains to be clearly demonstrated.[28,29] Because we used both vein patch angioplasty and anticoagulation therapy in all our IARs, we are unable to establish the effective influence of each of these factors in improving patency rates.

The incidence of limb loss was comparable for our female and male patients, a finding that correlates well with the situation reported in most series.[8-10,12-15] The type of conduit did not influence this outcome, probably because prosthetic grafts were only used in ~10% of the IARs in our series. Considering that 88.5% of our population (and >90% of the women) underwent IAR for limb salvage, the 10-year limb salvage rate of 93% in group I and 92% in group II clearly demonstrates the efficacy of the surgical procedure. This is important to note, in our opinion, especially because the role of endovascular procedures in the treatment of CLI is evolving. Their use, the degree of enthusiasm for them, and the related results have varied considerably over time, and now the endovascular approach has been suggested as the first-line therapy for most patients with PAD. Percutaneous treatments may be a less invasive alternative to open surgery, but even though comparable patency and limb salvage rates have been reported in female and male patients in the short-term and medium-term,[30] some concerns remain regarding the long-term durability of endovascular procedures in this setting.[31]

This study has several limitations. First, the analysis is limited naturally by its retrospective nature, even though the data were collected prospectively.

Second, the female and male patients differed in demographics, medical comorbidities, and clinical presentation. They were, however, comparable in the position and extent of anatomic lesions indirectly localizable by inflow sources and outflow target vessels, the type of conduit used, and postoperative foot care procedures, ensuring the technical homogeneity of the groups and the reliability of the results.

Finally, we acknowledge that our study may have been conducted on a relatively selected group that was not representative of the general population with CLI because it reflects a preliminary selection made by the physicians referring patients for revascularization at our institution (a tertiary care center with an interest and expertise in the management of CLI), who probably chose patients with a longer life expectancy, while recommending a conservative treatment (that ultimately leads to a major amputation in the majority of cases) for patients with multiple comorbidities and in worse general health.

CONCLUSIONS

IARs in female patients can achieve the same patency and limb salvage rates as those recorded in their male counterparts, and although the former may be older at presentation and need surgery for limb salvage more often than men, their outcome does not appear to be adversely affected.The skepticism surrounding the efficacy and durability of IAR in women appears to be unwarranted.

AUTHOR CONTRIBUTIONS

Conception and design: EB, AT
Analysis and interpretation: EB, MG, AT
Data collection: MG, RL, GP
Writing the article: EB, AT
Critical revision of the article: EB, GD, AT
Final approval of the article: EB, MG, RL, GO, GD, AT
Statistical analysis: GD
Obtained funding: Not applicable
Overall responsibility: EB

REFERENCES

1. Newman AB. Peripheral arterial disease: insights from population studies of older adults. J Am Geriatr Soc 2000;48:1157-62.
2. Stefánska A, Sypniewskay G, Senterkiewicz L. Inflammatory markers and cardiovascular risk in healthy polish women across the menopausal transition. Clin Chem 2005;51:1893-5.
3. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.
4. Higgins JP, Higgins JA. Epidemiology of peripheral arterial disease in women. J Epidemiol 2003;13:1-14.
5. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the national health and nutrition examination survey, 1999-2000. Circulation 2004;110: 738-43.
6. Zheng ZJ, Rosamond WD, Chambless LE, Nieto FJ, Barnes RW, Hutchinson RG, et al. Lower extremity arterial disease assessed by ankle-brachial index in a middle-aged population of African Americans and whites: the Atherosclerosis Risk in Communities (ARIC) study. Am J Prev Med 2005;29;Suppl 1:42-9.
7. Eugster T, Gürke L, Obeid T, Stierli P. Infrainguinal arterial reconstruction: female gender as risk factor for outcome. Eur J Vasc Endovasc Surg 2002;24:245-8.
8. Roddy SP, Darling RC 3rd, Maharaj D, Chang BB, Paty PS, Kreienberg PB, et al. Gender-related differences in outcome: an analysis of 5880 infrainguinal arterial reconstructions. J Vasc Surg 2003;37:399-402.
9. Harris EJ, Taylor LM, Moneta GL, Porter JM. Outcome of infrainguinal arterial reconstruction in women. J Vasc Surg 1993;18:627-36.
10. Mays BW, Towne JB, Fitzpatrick CM, Smart SC, Cambria RA, Seabrook GR, et al. Women have increased risk of perioperative myocardial infarction and higher long-term mortality rates after lower extremity arterial bypass grafting. J Vasc Surg 1999;29:807-13.
11. Bruni KR, Bagramian A, Cullen C, Rossi M, Shah DM, Darling RC 3rd, et al. Outcome after distal vascular reconstruction in women. J Vasc Nurs 1999;17:29-31.
12. Frangos SG, Karimi S, Kerstein MD, Harpavat M, Sumpio B, Roberts AB, et al. Gender does not impact infrainguinal vein bypass graft outcome. Surgery 2000;127:679-86.
13. Magnant JG, Cronenwett JL, Walsh DB, Schneider JR, Besso SR, Zwolak RM. Surgical treatment of infrainguinal arterial occlusive disease in women. J Vasc Surg 1993;17:67-78.
14. Belkin M, Conte MS, Donaldson MC, Mannick JA, Whittemore AD. The impact of gender on the results of arterial bypass with in situ greater saphenous vein. Am J Surg 1995;170:97-102.
15. AhChong AK, Chiu KM, Wong M, Yip AW. The influence of gender difference on the outcomes of infrainguinal bypass for critical limb ischaemia in Chinese patients. Eur J Vasc Endovasc Surg 2002;23: 134-9.
16. Enzler MA, Ruoss M, Seifert B, Berger M. The influence of gender on the outcome of arterial procedures in the lower extremity. Eur J Vasc Endovasc Surg 1996;11:446-52.
17. Ballotta E, Renon L, De Rossi A, Barbon B, Terranova O, Da Giau G. Prospective randomized study on reversed saphenous vein infrapopliteal bypass to treat limb-threatening ischemia: common femoral artery versus superficial femoral or popliteal and tibial arteries as inflow. J Vasc Surg 2004;40:732-40.
18. Connors JP, Walsh DB, Nelson PR, Powell RJ, Fillinger MF, Zwolak RM, et al. Pedal branch artery bypass: a viable limb salvage option. J Vasc Surg 2000;32:1071-9.
19. Ballotta E, Da Giau G, Gruppo M, Mazzalai F, Martella B. Infrapopliteal arterial revascularization for critical limb ischemia: is the peroneal

artery at the distal third a suitable outflow vessel? J Vasc Surg 2008;47:952-9.
20. Ballotta E, Renon L, Toffano M, Piccoli A, Da Giau G. Patency and limb salvage rates after distal revascularization to unclampable calcified outflow arteries. J Vasc Surg 2004;39:539-46.
21. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517-38.
22. Egorova N, Vouyouka AG, Quin J, Guillerme S, Moskowitz A, Marin M, et al. Analysis of gender-related differences in lower extremity peripheral arterial disease. J Vasc Surg 2010;51:372-9.
23. Harthun NL, Cheanvechai V, Graham LM, Freischlag JA, Gahtan V. Arterial occlusive disease of the lower extremities: do women differ from men in occurrence of risk factors and response to invasive treatment? J Thorac Cardiovasc Surg 2004;127:318-21.
24. Eslami MH, Zayaruzny M, Fitzgerald GA. The adverse effects of race, insurance status, and low income on the rate of amputation in patients presenting with lower extremity ischemia. J Vasc Surg 2007;45:55-9.
25. Vogt MT, Cauley JA, Kuller LH, Nevitt MC. Functional status and mobility among elderly women with lower extremity arterial disease: the Study of Osteoporotic Fractures. J Am Geriatr Soc 1994;42:923-9.
26. Hendel RC, Chen MH, L'Italien GJ, Newell JB, Paul SD, Eagle KA, et al. Sex differences in perioperative and long-term cardiac event-free survival in vascular surgery patients. Circulation 1995;91:1044-51.
27. Flinn WR, Rohrer MJ, Yao JS, McCarthy WJ III, Fahey VA, Bergan JJ. Improved long-term patency of infragenicular polytetrafluoroethylene graft. J Vasc Surg 1988;7:685-90.
28. Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral anticoagulants or Aspirin study): a randomised trial. Lancet 2000;355:346-51.
29. Johnson WC, Williford WO; members of the Department of Veterans Affairs Cooperative Study # 362. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. J Vasc Surg 2002;35:413-21.
30. DeRubertis BG, Vouyouka A, Rhee SJ, Califano J, Karwowski J, Angle N, et al. Percutaneous intervention for infrainguinal occlusive disease in women: equivalent outcomes despite increased severity of disease compared with men. J Vasc Surg 2008;48:150-8.
31. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischemia of the leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patient randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51(5 Suppl):5S-17S.

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